REMARKS/ARGUMENTS

With this amendment, claims 10-13, and 17-29 are pending. Claims 1-9 and 14-16 are withdrawn. For convenience, the Examiner's rejections are addressed in the order presented in an April 30, 2007, Office Action.

I. Status of the claims

Claims 10 and 17 are amended to recite that the pharmaceutical compositions are administered to an infected mammalian subject in an amount effective to inhibit the growth of an infecting bacteria. Support for these amendments is found throughout the specification, for example at paragraphs 70, 72, and 74. Claims 10 and 17 are also amended to recite that early lysis of the infecting bacteria by the holin-modified bacteriophage and a reduced production of phage particles by the holin-modified bacteriophage reduces an anti-phage immune response in the human subject. Support for these amendments is found throughout the specification, for example at paragraphs 80, and 83. Claims 10 and 17 also recite administration of the pharmaceutical composition to an infected mammalian subject. New claim 30 depends from claims 10 and 17 and recites that the mammalian subject is a human subject. Support for these amendments is found throughout the specification, for example at paragraphs 70 and 103. These amendments add no new matter.

II. Claim objections

Claim 27 is objected to because of use of the word "ins". Claim 27 is amended to recite "in", rather than "ins". In view of this amendment, withdrawal of the objection to claim 27 is respectfully requested.

III. Rejections under 35 U.S.C. §103(a)

The claims are variously rejected under § 103(a) as being unpatentable over the disclosure of Johnson-Boaz et al. ("Johnson-Boaz") either taken alone or in combination with Ghanbari et al. ("Ghanbari"), Clark et al. ("Clark"), Taylor et al. ("Taylor") and/or Vukov et al.

("Vukov"). Each rejection thus relies upon the Johnson-Boaz publication as the primary reference. This rejection is respectfully traversed for at least the reasons set forth below.

We first provide a brief review of the relevant law, and then an analysis of the facts of the case at hand.

The law of obviousness requires that the differences between the prior art and the claimed invention be evaluated at the time the invention was made, and without benefit of Applicants' disclosure

As set forth in MPEP § 2141 (I),[1] the four factual inquires for determining obviousness are as follows:

(A) Determining the scope and contents of the prior art;

(B) Ascertaining the *differences between the prior art and the claims in issue*;

(C) Resolving the level of ordinary skill in the pertinent art; and

(D) Evaluating evidence of secondary considerations.

In assessing the scope and content of the prior art, references must be considered in their entirety, i.e., as a whole including portions that would lead away from the claimed invention.[2] And, the differences between the claimed invention and the prior art must be evaluated "at the time the invention was made" in order to avoid impermissible hindsight.[3] Moreover, the claimed invention must be considered as a whole and an assessment made as to whether there exists a reasonable expectation of success in combining the cited references.[4]

A prima facie case of obviousness requires an Examiner to provide an explicit reason why the skilled worker would combine the known elements in the fashion claimed by Applicant

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[1] *Citing Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966).

[2] *See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); *see also* MPEP § 2141.02.

[3] 35 U.S.C. § 103(a) states:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, ***if the differences*** between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious ***at the time the invention was made*** to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made (emphasis added).

[4] *See* MPEP § 2141.

The Patent Office bears the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103.[5] To support a rejection under § 103 using the Federal Circuit's teaching-suggestion-motivation (TSM) test, the Office must provide evidence that demonstrates some suggestion or motivation to modify or combine the references, whether in the references themselves or in the knowledge generally available to one of ordinary skill in the art.[6] Next, the Office must show that one of ordinary skill in the art would have had a reasonable expectation of success in modifying the prior art references, or in combining their relevant teachings.[7] Finally, the Office must show that the combined prior art references "teach or suggest all the claim[ed] limitations."[8]

Recently, in reviewing this standard, the Supreme Court noted that any analysis supporting a rejection under § 103(a) must be made explicit, and that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the manner claimed."[9] "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."[10]

The teaching or suggestion to make the claimed combination *and* the reasonable expectation of success must both be found in the prior art, and ***not*** based on applicant's disclosure.[11] The Examiner's suggestion of the desirability of doing what the inventor has done must be found either expressly or impliedly in the references, or supported by a convincing line of reasoning, which must rely on logic and sound scientific reasoning.[12]

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[5] *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988); *In re Duel*, 51 F.3d 1557 (Fed. Cir. 1995).
[6] *Fine*, 837 F.2d at 1074; MPEP § 2143.
[7] *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).
[8] MPEP § 2143.
[9] *KSR Intl Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007).
[10] *Id.*
[11] *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).
[12] *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). *See also* MPEP § 2144; and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (requiring reliance on logic and sound scientific reasoning in supporting a conclusion of obviousness).

While the Court warned against a "rigid application"[13] of the TSM test, the Court also found that these questions could provide a "helpful insight" in determining whether the claimed subject matter is obvious under § 103(a).[14]

An Examiner's claimed combination cannot change the principle of operation of the primary reference or render the reference inoperable for its intended purpose

If the Examiner's proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.[15] Further, if references taken in combination would produce a 'seemingly inoperative device,' the Federal Circuit has held that such references teach away from the combination and thus cannot serve as predicates for a *prima facie* case of obviousness.[16]

We now turn to the rejections of record.

The Johnson-Boaz reference either alone or in combination with Ghanbari, Clark, Taylor or Vukov does not render the claimed invention obvious

Each of the prior art rejections of record rely upon the Johnson-Boaz publication as a primary reference:

- Claims 10 and 17-21 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Johnson-Boaz et al.
- Claims 17 and 22 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Johnson-Boaz et al. in view of Ghanbari et al. (U.S. Patent No. 6,121,036).
- Claims 10-13, 28 and 29 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Johnson-Boaz et al. in view of Taylor et al. and Clark et al. (U.S. Patent No. 2,851,006).
- Claims 10 and 23-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Johnson-Boaz et al. in view of Vukov et al.

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[13] *KSR*, at 1396-7.
[14] *KSR* at 1396. *See also*, Memorandum to Technology Directors from Margaret A. Focarino, Deputy Commissioner for Patent Operations, May 3, 2007.
[15] *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984) (inoperable modification teaches away); MPEP § 2143.01.

In rejecting claims 10 and 17-21 as allegedly obvious over Johnson-Boaz, the Examiner cites case law for the proposition that mere purity of a product, by itself, does not render a product unobvious.[17]

Yet, MPEP § 2144.04 (VII) advises Examiners that pure materials are novel vis-à-vis less pure or impure materials because there is a difference between pure and impure materials. Factors to be considered in determining whether a purified form of a known product is obvious over the prior art include whether the claimed chemical compound or composition has the same utility as closely related materials in the prior art, and whether the prior art suggests the particular form or structure of the claimed material or suitable methods of obtaining that form or structure. [18]

Here, independent claim 10 specifies that the *holin*-modified bacteriophage is administered in conjunction with "a pharmaceutically acceptable carrier suitable for administration to an infected mammalian subject." The utility of the claimed *holin*-modified phage therapeutic versus the utility of the missense mutation in the *holin* gene observed in Johnson-Boaz is different. Johnson-Boaz state that the mutation of Ala to Gly at position 52 in the primary sequence of the Holin protein may be useful for *studying* the molecular mechanism of *holin* temporal regulation. (p. 501; para. 2). Nowhere do the authors contemplate administering such a modified phage to a mammalian subject, *e.g.*, a human subject. The reference is not concerned with the possible effects such a genetically-modified phage could have in a mammal, or that it would need to be administered in conjunction with "a pharmaceutically acceptable carrier suitable for administration to an infected mammalian subject." Neither does the reference suggest the particular form or structure of the claimed material, nor methods of obtaining that form or structure, such as the requirement that the composition be "at least 60% by weight free from proteins and naturally-occurring organic

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[16] *In re Sponnoble*, 405 F.2d 578, 587, 160 USPQ 237, 244, 56 C.C.P.A. 823 (1969).
[17] *Ex parte Gray*, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989).
[18] *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966) (claims to the free-flowing crystalline form of a compound were held unobvious over references disclosing the viscous liquid form of the same compound because the prior art of record did not suggest the claimed compound in crystalline form or how to obtain such crystals).

molecules" as specified in claim 17. Accordingly, Applicants' purified pharmaceutical form of a structurally-modified bacteriophage is nonobvious over the cited art.

Johnson-Boaz fails to teach or suggest a holin-modified bacteriophage that would provide for early lysis at a temperature relevant to its use as a pharmaceutical composition, as encompassed by the present claims. Specifically, the temperature sensitive bacteriophage of Johnson-Boaz exhibit early lysis at 42°C, a temperature above that maintained by most mammals. For example, human body temperature is 37°C. Even at a very high temperature that may be associated with fever in a human subject (e.g., 40°C or 104°F) is still below the 42°C temperature of induction disclosed in Johnson-Boaz.

Applicant notes that in order to meet its burden in establishing a rejection under § 103 the Office must demonstrate that the cited art teaches or suggests all the claim limitations.[19] Specifically, independent claims 10 and 17 require that early lysis reduce the anti-phage immune response in a mammalian subject. Nowhere does the Johnson-Boaz publication show or suggest this claimed feature. The reference does not teach administration of a *holin*-modified bacteriophage to a mammalian subject, let alone that such a modification could reduce the anti-phage immune response in a mammalian subject. There is also no teaching in the reference regarding other methods by which the *holin* gene may be modified. The reference focuses solely on creating a missense allele of Ala to Gly at position 52. The claimed subject matter is not a routine variation of Johnson-Boaz given that the reference does not show or suggest that early expression of *holin* can reduce the anti-phage immune response in a mammal, and in particular in a human subject. Accordingly, the independent claims and their dependencies are not unpatentable over Johnson-Boaz.

With respect to claims 17 and 22, the Examiner acknowledges that Johnson-Boaz alone does not form a basis for obviousness as it "does not specifically contemplate a composition comprising both phage and an antibiotic." The Ghanbari reference was cited to compensate for the absence of this teaching in the primary reference. However, as it was cited merely for its alleged teaching of methods of preparing a purified, toxin-free phage preparation, Ghanbari cannot compensate for the deficiencies of the primary reference. Nowhere does

Ghanbari disclose a purified form of the composition, or a composition that reduces the anti-phage immune response in a mammalian subject. Accordingly, claims 17 and 22 are not unpatentable over Johnson-Boaz in view of Ghanbari.

The Examiner also acknowledges that Johnson-Boaz alone does not render claims 10-13 and 28-29 obvious as the reference "does not teach a lyophilized form of phage or a composition of two or more different *holin*-modified bacteriophages that affect inhibition of a least two different bacterial hosts." Taylor and Clark were cited merely for their alleged teaching of cocktails of phages and methods of preparing a lyophilized phage composition for storage purposes, respectively. As above, the references do not cure the deficiencies of the primary reference. Nowhere do they show or suggest a purified form of the composition, or a composition that reduces the anti-phage immune response in a mammalian subject. Accordingly, claims 10-13, 28 and 29 are not unpatentable over Johnson-Boaz in view of Taylor and Clark.

The Examiner also notes that the Johnson-Boaz reference alone does not render obvious claims 10 and 23-27 as it "does not teach a *holin*-modified phage comprising a non-endogenous *holin* gene operably linked to a promoter (or an inducible promoter) that facilitates early expression." The Examiner applies a second reference, stating that one would have been motivated to "modify the phage of Johnson-Boaz to produce a recombinant phage with exogenous *holin* genes as taught by Vukov."

The claims specify that the invention reduces the anti-phage immune response in a mammalian subject. This feature indicates that the composition may eliminate or minimize the development of an immune response against the phage itself when it is used for treating bacterial infections. Nowhere does Vukov show or suggest the composition claimed wherein early lysis reduces the mammalian anti-phage immune response.

Furthermore, the Vukov reference discloses a system for qualitatively evaluating the functional properties of *holin* genes in a variety of bacteria. Nowhere does the reference show or suggest the use of an early expression or inducible promoter, such as T7. Rather, the reference describes the thermal induction (p. 183; FIG. 1) of bacteria lysogenized with different alleles of the phage *holin* gene. Early lysis was assessed after a temperature shift (p. 181), which

[19] MPEP § 2143.

one of skill would never employ in the context of a therapeutic, in particular a therapeutic for administration to a human subject.

The law states that if, in assessing obviousness under 35 U.S.C. § 103(a), the Examiner's proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.[20]

The Examiner posits that "there would have been a reasonable expectation of success given the fact that Vukov successfully produced recombinant phage with heterologous *holin* genes." Applicants must respectfully disagree. The claimed composition is intended for use in a mammalian subject. Vukov teach a *holin* construct that takes advantage of the gene's native temperature-sensitive CIts857 repressor. At 30 °C the repressor functions normally, and from about 37 °C to about 42 °C it is inactivated. *See* U.S. Patent No. 4,582,800. Vukov disclose reagents wherein the *holin* promoter is repressed (turned-off) at 30 °C and derepressed (turned-on) at 42 °C. Accordingly, under the Vukov method, the temperature in a mammalian subject, *e.g.*, a human subject, would literally need to be increased beyond survivability to induce early Holin protein production and provide a "therapeutic benefit".

An Examiner's reasoning supporting a finding of obviousness must be set forth with explicit evidence.[21] Here, the Examiner's suggested combination would frustrate the purpose of Applicants' invention. Thus, there is no explicit evidence that one of skill would have been motivated to make the proposed modification. Because the Examiner has neither established a *prima facie* case of obviousness, nor presented explicit evidence that one of skill would have been motivated to make the proposed modification, the invention cannot be obvious in view of the cited art and the rejection may be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

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[20] *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); MPEP § 2143.01.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Beth L. Kelly
Reg. No. 51,868

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
BLK:blk
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[21] *KSR Intl Co.*, at 1396.